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(54) Title: INHIBITION OF INTRAOPERATIVE MIOSIS/PRODUCTION OF MYDRIASIS BY LOCAL ANESTHETICS

(57) Abstract

This invention relates to a method for inhibiting intraoperative miosis or producing intraoperative mydriasis wherein a local anesthetic is introduced into an intraocular chamber of a subject undergoing intraocular surgery. Kits are provided for supplying the surgeon with an ophthalmologically-acceptable solution containing an effective amount of the local anesthetic.

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INHIBITION OF INTRAOPERATIVE MIOSIS/PRODUCTION OF MYDRIASIS BY LOCAL ANESTHETICS

Field of the Invention

This invention relates to a method for inhibiting intraoperative miosis or producing intraoperative mydriasis, wherein a local anesthetic is introduced into an intraocular chamber of a subject undergoing intraocular surgery. Kits are provided for supplying the surgeon with an ophthalmologically-acceptable solution containing an effective amount of the local anesthetic.

Background of the Invention

During intraocular surgery, particularly during the removal of the cataractous lens, a small pupil in the operative eye can impair the work of the ophthalmic surgeon. A smaller pupil generally is found in older subjects, those individuals most frequently undergoing intraocular surgery. Moreover, the pupil becomes constricted or miotic when the eye is opened for surgery. Manipulation of intraocular instruments and the lens material is difficult when the pupil is miotic.

In order to maintain a desirable operative field during intraocular surgery, constriction of the pupil should be prevented, inhibited or reversed or dilation of the pupil (mydriasis) should be accomplished. Mechanical devices for physically retracting the pupil during surgery have been proposed. See, e.g. U.S. Patents Nos. 4,991,567 and 4,782,820. Positioning of these devices, however, is time-consuming, and such devices are not suitable for many intraocular surgical procedures involving delicate movements of instruments and tissues.

Pharmacological agents have been sought for inhibiting miosis or producing mydriasis. Before surgery, topical non-steroidal anti-inflammatory agents have been applied to prevent intraoperative miosis, but this treatment is only minimally effective. (Keates et al Ann. Ophthalmol. 16(10) 919-921 (1984) It is known that the pupil dilates during retrobulbar anesthesia but that this dilation is subsequently lost. During surgery, epinephrine has been added to intraocular irrigating solutions, but this drug does not often reverse miosis or produce mydriasis to a significant extent. Lotti (U.S. patent no. 5,153,205) teaches topical application of cholinergic M3 receptor antagonists to inhibit miosis. Nagy (U.S. patent no. 4,960,799) teaches topical administration of beta-blockers to treat inflammation of the eye and discloses that the

beta-blockers also inhibit miosis during eye surgery. Bock et al. (U.S. patent no. 5,218,114) disclose that cholecystokinin antagonists may be used during intraocular surgery to prevent miosis.

The effectiveness of certain of the foregoing compounds for inhibiting miosis or producing mydriasis during intraocular surgery is not accepted by those skilled in the art. None are used universally.

Certain local anesthetics have been applied topically to the eye for achieving corneal anesthesia and for permitting tonometry. They further have been injected behind the eye as retrobulbar anesthetics. The use of local anesthetics as inhibitors of miosis also has been explored. Their usefulness as inhibitors of miosis, however, remains controversial.

Several investigators have reported on the topical and intracameral effects of local anesthetics on miosis. Some investigators reported that certain local anesthetics caused mydriasis or blocked miosis that was associated with laser irradiation or that was chemically induced. (See Butler, J., Exp. Eye Res. 28: 1979, 577-589; Norden, L., J. Am Optom. Assoc. 47: 1976, 730-733; Unger, W., Exp. Eye Res. 25: 1977; 209-220; Unger, W., Ophthalmologica 175: 1977; 153-158; Sears, M., Archives of Ophthalmol. 63: 1960; 159-166; and Spenser, R., J. Pharmacol. Exp. Ther. 113: 1955; 421-430.)

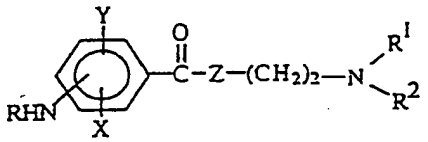
Conversely, several investigators have reported that some of these same or other local anesthetics do not cause mydriasis or do not block miosis associated with laser irradiation (See Emmerich, R., Am. J. Ophthalmol, 40: 1955, 841-848; Lyle, W., Amer. J. Optom. & Physiol. Optics, 54: 1977, 276-281; Rosenwasser, G., Int. Ophthalmol. Clin., 29: 1989; Schlegel, H., Arch. Ophthalmol. 51: 1954; 663-670; Unger, W., Exp. Eye Res., 25: 1977; 209-220.)

Perhaps the reason that local anesthetics are not applied topically or intracamerally routinely in ophthalmic procedures is the body of work indicating that local anesthetics can be toxic to the eye. (See Bryant, Survey of Ophthal., 13: 1969; 263-283; Burstein, N., Survey of Ophthalmol., 25: 1980; 15-30; Norden, L., J. Am. Optom. Assoc., 47: 1976, 730-733.)

2-Chloroprocaine is a local anesthetic which has never been tested as a blocker of miosis. It is hydrolyzed very quickly and is unstable in commercially available ophthalmic buffer systems.

Summary of the Invention

It has been discovered that a particular class of local anesthetics can inhibit miosis associated with intraocular surgery without the adverse side effects characteristic of the local anesthetics discussed above. This class of local anesthetics are halogen substituted esters that hydrolyze quickly in the environment of the eye. They are particularly labile on and around the cornea, as a result of the presence of pseudocholinesterase in the corneal epithelium and endothelium. These halogen substituted esters that are local anesthetics are defined by the general formula as follows.



where R is hydrogen or lower alkyl (1 to 4 carbon atoms, straight chain), R^1 is hydrogen or lower alkyl (1-4 carbon atoms, straight chain), R^2 is lower alkyl (1-4 carbon atoms) and may be straight chain or branched, X and Y are independently hydrogen, chloro or bromo, Z is oxygen or sulfur and with the proviso that the amino group (RHN-) may be present or absent and if present is substituted in the 3 or 4 position of the benzene ring.

According to one aspect of the invention, a method for inhibiting intraoperative miosis or producing intraoperative mydriasis is provided. An effective amount of a halogen substituted ester local anesthetic defined by the foregoing general formula is introduced into an intraocular chamber of a subject, substantially simultaneously with performing intraocular surgery on the subject. The preferred local anesthetic for use in the present invention is 2-chloroprocaine hydrochloride.

In some embodiments, the halogen substituted ester local anesthetic is introduced into the intraocular chamber by instillation of a pharmacologically acceptable carrier containing said local anesthetic in the chamber. Preferably the local anesthetic is introduced into the intraocular chamber by perfusing the chamber with an intraocular irrigating solution containing the local anesthetic. The intraocular irrigation solution may contain the local anesthetic at a concentration of about 1 micromolar to 100 millimolar, but preferably at 0.1mM to 10.0mM. Most preferably,

the intraocular irrigating solution contains 2-chloroprocaine hydrochloride at a concentration of 0.1mM to 10mM, and the intraocular irrigating solution is free of a phosphate buffer.

The present invention also includes kits for intraocular surgery. In certain preferred embodiments, the kits comprise a package including a first container containing a first amount of an ophthalmologically acceptable carrier, the first amount being between 10ml and 1000 ml. The package also includes a second container containing a labile ester such as a halogen substituted ester local anesthetic in a concentrated amount. When the first amount is mixed with the concentrated amount to produce a therapeutic solution, that solution is opthalmologically acceptable. If the ester is a local anesthetic, the local anesthetic is present in the solution at a concentration effective for inhibiting surgical miosis or producing intraoperative mydriasis when introduced into an intraocular chamber.

In other preferred embodiments, the kit comprises a package including a first container containing a first amount of an intraocular irrigation solution, wherein the solution is incomplete with respect to one or more irrigant components. The first amount is between 100ml and 1000ml. The package also includes a housing containing a halogen substituted ester local anesthetic in a concentrated amount and containing said one or more irrigant components in a supplement amount. When the first amount is mixed with the concentrated amount and with the supplement amount to produce a therapeutic solution, the local anesthetic is present in the solution at a concentration effective for inhibiting surgical miosis or producing intraoperative mydriasis when introduced into an intraocular chamber and said solution is pH and osmotically compatible with intraocular tissues. In this embodiment, the housing may be a second container containing both the local anesthetic and the one or more irrigant components. The housing also can be a second and a third container, the second container containing the local anesthetic and the third container containing the one or more irrigant components.

The kits of the invention may include, in addition, instructions for preparation of the therapeutic solution and for use of the solution in connection with intraocular surgery, and in particular to inhibit miosis or produce intraoperative mydriasis during intraocular surgery.

The intraocular solutions used in the invention are water solutions containing irrigant components preferably including sodium ions, potassium ions, calcium ions, magnesium ions, chloride ions, acetate ions, bicarbonate ions, citrate ions, dextrose and glutathione disulfide.

Certain local anesthetics useful in the invention cannot be stored for any extended period of time in known ophthalmic solutions, including known two part solutions. It has been

discovered that 2-chloroprocaine is unstable for extended periods in nonacidic solutions at neutral pH, is unstable for short periods in the presence of a phosphate buffer, and is unstable even in an acidic solution if that acidic solution contains dextrose. All of the foregoing are typical components of one or two part ophthalmic solutions.

According to another aspect of the invention, a two part ophthalmic solution is provided. This solution includes an acidic component and a nonacidic component. A labile ester such as a halogen substituted ester local anesthetic is contained in the acidic component which is free of dextrose. The acidic component can include glutathione and can be a solution or a powder. The nonacidic component includes a nonphosphate buffer, preferably selected from the group consisting of acetate, bicarbonate, carbonate and citrate, or combinations thereof. The two components, when mixed together, preferably form an ophthalmologically acceptable solution for use as an ophthalmic irrigant. The preferred final pH is neutral, preferably at about 7.4. The two parts can be provided in the kits of the invention.

The present invention also sets forth a device comprising a bottle containing an intraocular solution and a halogen substituted ester local anesthetic present in an amount effective for inhibiting miosis or producing intraoperative mydriasis when perfused or instilled into an intraocular chamber of an eye during intraocular surgery. The bottle contains between 10ml and 1000ml of the intraocular solution containing the halogen substituted ester local anesthetic, preferably at a concentration between 0.1mM and 10mM. The intraocular solution is ophthalmologically acceptable, including being pH compatible and iso-osmotic with the eye.

Other features and advantages of the invention will be apparent from the following description and from the claims.

Brief Description of the Drawings

Figure 1 is a graph illustrating the effect on pupil size of intraocular perfusion with an irrigant containing 1mM of the local anesthetic 2-chloroprocaine hydrochloride.

Figure 2 is a graph illustrating the effect on post-operative intraocular pressure of intraocular perfusion with an irrigant containing 2-chloroprocaine hydrochloride.

Figure 3 is a graph illustrating the effect on post-operative pupil size of intraocular perfusion with an irrigant containing 1mM of the local anesthetic 2-chloroprocaine hydrochloride.

Detailed Description of the Invention

This invention encompasses methods for inhibiting intraocular surgical miosis or producing intraoperative mydriasis by delivering a halogen substituted ester local anesthetic to an intraocular chamber of an eye undergoing surgery. Intraoperative miosis and surgical miosis are used interchangeably herein. Miosis means the constriction of the pupil. Miosis occurs during standard intraocular operative procedures which involve mechanical contact with ocular tissue and manipulation of ocular components. The resultant small pupil size hinders the view of the surgeon, minimizes access to the intraocular cavity, and may force modification of the surgical technique. Inhibition of miosis is achieved by preventing, inhibiting or reversing the iris muscle contraction which causes a small pupil during intraocular surgery.

Mydriasis is an abnormal dilation of the pupil. Mydriasis can be useful intraoperatively by maximizing access to the intraocular cavity.

It has been discovered that halogen substituted ester local anesthetics are capable of inhibiting intraocular surgical miosis or producing intraoperative mydriasis when applied to an intraocular chamber substantially simultaneously with surgery. The use of such anesthetics avoids side effects characteristic of other anesthetics. The miosis may be neurogenic in origin and thus may be due to an axon reflex. While not limiting the treatment of this invention to the validity of one proposed mechanism of action, it is believed that the local anesthetics, when introduced into an intraocular chamber, decrease the ability of the pupil to constrict by blocking the neuronal conduction of electrical impulses by nerves within the eye and release of mediators or transmitters, presumably in communication with the iris.

Intraocular chamber means a space within the eyeball which is bordered by characteristic tissues forming an identifiably separate region. The eye is comprised of three chambers: the anterior chamber, the posterior chamber and the vitreous chamber. In the method of the present invention wherein local anesthetics are introduced into an intraocular chamber to inhibit miosis, it is believed important that the local anesthetic contact the nerves that activate the iris reflex. Although it is believed that the nerves activating iris contraction reside mainly in the tissue surfaces of the anterior and posterior chamber, they may travel as well to more remote intraocular surfaces such as those defining the vitreous chamber. In the present invention, the halogen substituted ester local anesthetics preferably are brought into contact with tissues forming the anterior and posterior chamber surfaces.

The method of the invention is for treatment of eyes of mammalian subjects (e.g.,

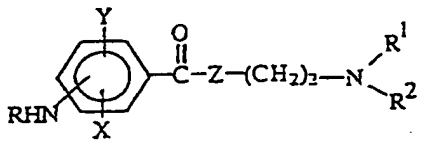
humans, non-human primates, dogs, cats, horses, sheep, goats, cows, pigs and rodents). Surgical procedures for which this invention is useful include, but are not limited to, the manipulation or the removal of the cataractous lens, phacoemulsification, the manipulation, insertion and/or removal of a prosthetic intraocular lens, pars plana vitrectomy, vitreal surgery, retinal surgery, extracapsular or intracapsular cataract extraction/lens aspiration and anterior segment reconstruction.

The compounds useful in practicing the invention are halogen substituted ester local anesthetics. The term "local anesthetics" is an art recognized term and applies to drugs that block nerve conduction when applied locally to nerve tissue in appropriate concentrations. They act on any part of the nervous system and on every type of nerve fiber. Their action, however, is reversible in that their discontinuation is followed by complete recovery in nerve function.

Typical local anesthetics contain hydrophilic and hydrophobic domains that are separated by an intermediate alkyl chain. The hydrophilic domain usually is a tertiary amine, but can also be, among other things, a secondary amine. The hydrophobic domain typically is an aromatic residue. Hydrophobicity increases potency and duration of action, but also potential toxicity.

The local anesthetics useful according to this invention are halogen substituted esters of the following general formula. These particular local anesthetics are highly labile, but nontoxic to the eye. They are particularly nontoxic to the eye due to the presence of pseudocholinesterase at the corneal endothelium, which actively degrades the ester bond. Toxicity is thereby considerably reduced.

The structure of the local anesthetics useful in the invention is depicted as follows.



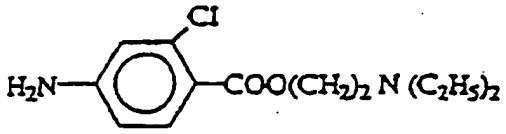
where R is hydrogen or lower alkyl (1 to 4 carbon atoms, straight chain), R^1 is hydrogen or lower alkyl (1–4 carbon atoms, straight chain), R^2 is lower alkyl (1–4 carbon atoms), and may be straight chain or branched, X and Y are independently hydrogen, chloro or bromo, Z is oxygen or sulfur and with the proviso that the amino group (RHN-) may be present or absent and if present

is substituted in the 3 or 4 position of the benzene ring.

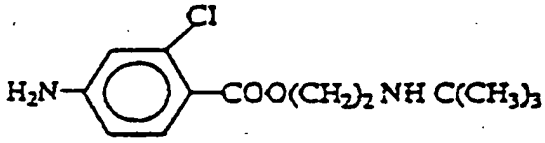
Examples of halogen substituted ester-type local anesthetics include, but are not limited to the following.

Halogen Substituted Ester-Type Local Anesthetics

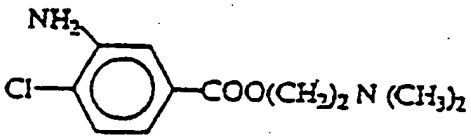
2-Chloroprocaine



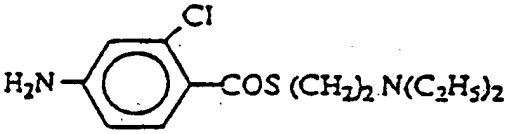
2-tert-butylaminoethyl-2 chloro-4-amino benzoate



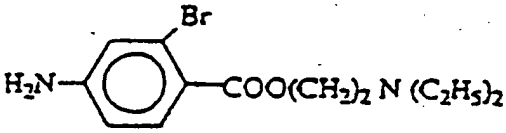
Clormecaine



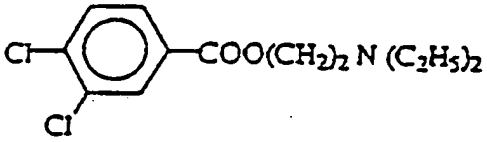
2-chlorothiocaine



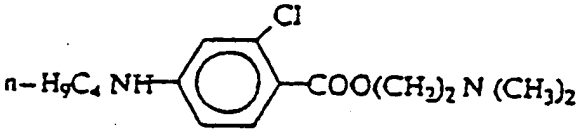
2-Bromoprocaine



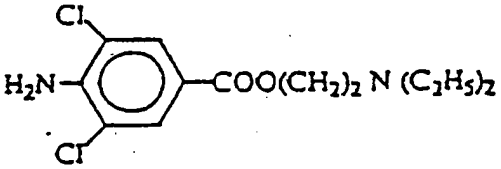
2-diethlyaminoethyl-3,4 dichlorobenzoate



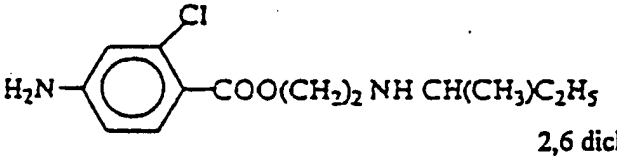
2-Chlorotetracaine



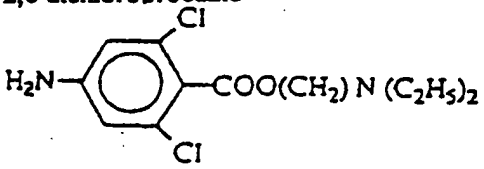
3,5 dichloroprocaine



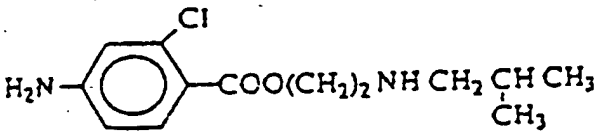
2-sec-butylaminoethyl-2- chloro-4-amino-benzoate



2,6 dichloroprocaine



2-isobutylaminoethyl-2- chloro-4-amino-benzoate



Mixtures of long and short acting anesthetics also are contemplated by the invention. Also embraced by the invention are compounds typically classified under other categories of drugs as a result of another known activity, but which are demonstrated to have short acting local anesthetic activity such as certain beta blockers and certain antihistamines.

Pharmaceutically acceptable salts of local anesthetics include the conventional non-toxic salts formed from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, nitric and the like; and the salts prepared from organic acids such as acetic, proprionic, succinic, glycolic, stearic, lactic, maleic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, formic, malonic, naphthalene-2-sulfonic, benzenesulfonic and the like.

The local anesthetics are introduced into an intraocular chamber in ophthalmologically acceptable amounts and in ophthalmologically acceptable solutions. Such amounts and solutions are those that cause no medically unacceptable side-effects when administered to an intraocular chamber of the eye according to the methods described herein. Preferred ophthalmologically acceptable solutions are sterile solutions which are approximately iso-osmotic with respect to the fluid in intraocular chambers. Such solutions are non-irritating to the eye and maintain the osmotic stability of the tissues defining the chamber. The osmolality preferably is between about 250 and about 350 mOsm and most preferably about 280-320 mOsm. The solutions also are pH compatible with the environment of the selected intraocular chamber. The pH of the solution preferably is between about 6.5 and about 8.0 and more preferably between about 7.2-7.8. Most preferably the pH is 7.4. The solutions optionally contain particular buffering agents and other factors to support metabolism in the eye tissue. For example, the solution may contain bicarbonate at a concentration of between about 10 and 50 mM/l. The solution also may contain, for example, dextrose (D-glucose) and glutathione. Other additives include sodium and potassium salts such as sodium and potassium chlorides, sulfates, acetates, citrates, lactates, and gluconates. Calcium and magnesium chlorides also may be added.

The halogen substituted ester local anesthetic is introduced into the intraocular chamber in an ophthalmologically acceptable carrier solution containing the local anesthetic at an effective concentration for inhibiting surgical miosis or producing intraoperative mydriasis. Introduced into the chamber means instilling it in the chamber or perfusing it in the chamber.

The solution containing the local anesthetic can be instilled in an intraocular chamber using a syringe at a time prior to the start of surgery or very early in the procedure. This instillation may be a single application of a small amount of carrier solution containing the local anesthetic. The solution also may be instilled into the chamber as a "wash", once or several times during the surgery.

The eye preferably is perfused during the course of the surgery with an ophthalmologically acceptable irrigation solution containing the halogen substituted ester local anesthetic. Perfusion is accomplished by means of a perfusing needle, cannula or probe which delivers in a sterile manner perfusing solution from a container. The cannula (as generally used in intraocular surgery) is capable of both providing the irrigation solution to the eye and also aspirating fluid thereby maintaining a clear field of operation for the surgeon.

The duration of action of the halogen substituted ester local anesthetic can influence the time at which the anesthetic is introduced into a chamber of the eye undergoing surgery. It is intended that the local anesthetic be applied substantially simultaneously with the surgical procedure. "Substantially simultaneously" means that the local anesthetic is introduced such that its effect coincides with the time during which the surgical procedure is being performed.

The duration of action of the halogen substituted ester local anesthetic will affect the choice of the local anesthetic and the method by which the local anesthetic is introduced into the intraocular chamber. Thus, a local anesthetic which is capable of exhibiting an effect for about a half hour or more (i.e., the entire time which may be needed to perform the eye surgery) may be introduced into an intraocular chamber in a single dose prior to or at the beginning of surgery. Those local anesthetics that have a somewhat shorter duration of action may need re-instillation, such as by a wash. In the preferred embodiment, however, the halogen substituted ester local anesthetics have a short duration of action and are introduced into the intraocular chamber by constant perfusion of an intraocular chamber during the course of surgery.

The local anesthetics of the invention are applied in effective amounts. An effective amount is that amount which prevents, inhibits or reverses miosis or produces mydriasis to a medically useful extent during intraocular surgery, (e.g., the operative field is improved for the surgeon or it is easier for the surgeon to manipulate surgical instruments and intraocular tissues). An effective amount is one controlled by a number of factors, including: the subject; the inherent anti-miotic or mydriatic activity of the local anesthetic; the amount of the local anesthetic used; its duration of action; and the method by which it is introduced into the

intraocular chamber, i.e., whether by a single application or by continuous perfusion. A perfusion solution having between 1 micromolar to 100mM of local anesthetic is believed to deliver an effective amount during intraocular surgery. Preferably perfusion solutions contain between 0.1mM to 10mM local anesthetic. It is important that the local anesthetics do not produce, at effective concentrations, long-term deleterious changes in the eye nor cause inflammation, discomfort or irritation. The determination of an effective dose for any selected compound is well within the level or ordinary skill in the art.

The present invention also includes kits providing a halogen substituted ester local anesthetic and a carrier for introducing the local anesthetic into an intraocular chamber during surgery. A carrier is an ophthalmologically acceptable solution in which the local anesthetic can be dissolved prior to application to an intraocular chamber. It is important that any solution applied to an intraocular cavity be free of any factors that would injure intraocular tissue. Thus it preferably is sterile, approximately iso-osmotic, at the correct pH and contains factors to support metabolism in the tissue, as described above.

The long-term effects of storage on the stability of the local anesthetics useful in the invention are problematic, particularly when the anesthetics are in aqueous solutions at neutral or alkaline pH. It further has been discovered that the preferred local anesthetic, 2-chloroprocaine, is unstable in phosphate buffer and in the presence of dextrose. Accordingly, it is an aspect of the invention that kits be provided for preparation of therapeutic solutions containing a local anesthetic within hours of surgery. In these kits, the local anesthetics can be in a stable powdered form or in a stable concentrated form such as concentrated in an acidic solution. The powdered or concentrated local anesthetic then can be dissolved or diluted in the ophthalmologically acceptable carrier solution immediately in advance of surgery.

The kits comprise a package, such as a box, blister pack or similar packing vehicle used conventionally to hold containers of liquid. The package may be coated with an impervious cover to assist in protecting the sterility of the contents during transport and storage. In the package are a container containing an amount of a carrier solution (or components thereof) and one or more containers containing a halogen substituted ester local anesthetic and any components missing from the carrier solution. The containers preferably are glass bottles, but may be formed of any inert material such as a rigid or flexible plastic in the form of bottles or bags that allow transport and storage of liquid without loss of fluid or contamination of the contents.

In certain preferred embodiments, the containers may be chambers in a single housing. In these embodiments the container may comprise in addition a structure to permit communication of the contents of the chambers without opening the container. In one such embodiment, the halogen substituted ester local anesthetic and the ophthalmologically acceptable carrier solution can be supplied in separate chambers of a two-chamber vial. Communication between the chambers can be provided by a frangible membrane. In use, the membrane is pierced or ruptured, with the carrier solution flowing into the chamber containing the local anesthetic (or vise versa). The local anesthetic, in powdered form or in a concentrated form, then is dissolved or diluted into the solution. In another embodiment, the upper and lower chambers are constructed and arranged within a syringe. Movement of the plunger causes the contents of the two chambers to mix.

In one aspect of the invention, the kit may be used to provide a carrier solution for instilling a single amount or wash amounts of a halogen substituted ester local anesthetic into an intraocular chamber. In these embodiments, the containers for the carrier solution preferably includes about 5ml to about 50ml of carrier solution. The container may be a bottle or vial with piercable septum. The local anesthetic may be supplied for example in a stable, concentrated solution (also in a bottle or vial with a piercable septum). In use, the septum of the bottle or vial containing the local anesthetic is pierced by the needle of a syringe and transferred to the bottle or vial containing the carrier solution. An ophthalmologically acceptable solution of predetermined anesthetic concentration effective for inhibiting surgical miosis or producing intraoperative mydriasis when introduced into an intraocular chamber is thereby formed. The solution then may be removed by syringe from the vial and instilled into the intraocular chamber.

In another aspect of the invention, the kit may be used to provide a carrier for perfusing a halogen substituted ester local anesthetic into an intraocular chamber during eye surgery. In these embodiments, the first container contains an intraocular irrigation solution (or components thereof) in an amount from about 100 to 1000ml, preferably about 500ml. Most preferably the first container is a bottle having a rubber septum which can be punctured by a needle attached to a tube for delivering the contents of the container to a perfusing needle and hence to the eye. Another container(s) includes a predetermined amount of the local anesthetic, and, in certain embodiments, components of the intraocular irrigation solution. The contents of the containers are mixed in a manner that maintains sterility to form an ophthalmologically acceptable solution containing the local anesthetic at a concentration effective for inhibiting surgical miosis when

perfused into an intraocular chamber during surgery.

As mentioned above, the solution contained in the first container may be only components of an intraocular irrigation solution. In other words, the intraocular irrigation solution may be "incomplete". One or more components of the intraocular irrigation solution may be provided in a second container with the halogen substituted ester local anesthetic or separately in a different container. Such arrangements can serve dual purposes. Firstly, certain components of the intraocular irrigation solution, such as organic components, may be more stable in concentrated form and at pHs other than physiological intraocular pH. Thus, as with the local anesthetic, the separation of such one or more components from the irrigation solution (and the local anesthetic solution) until the time of mixing just prior to surgery permits long term storage. Secondly, by providing important components in separate containers, a package may be constructed and arranged whereby an ophthalmologically acceptable irrigation solution is created only when all of the various contents of the different containers are mixed together. In this manner, the surgeon or medical staff supporting the surgeon will be inclined to use the materials as directed as opposed to substituting other materials which may not be as clinically desirable.

Thus, in certain preferred embodiments of the kit of the invention, the package includes a first container containing between 100ml and 1000ml of an intraocular solution, wherein the solution is incomplete with respect to one or more solution components. The package also includes a second container containing a halogen substituted ester local anesthetic and a third container containing said one or more solution components. In these embodiments, the contents of the first, second, and third containers are mixed together to form a solution which is pH and osmotically compatible with the intraocular environment of an eye and in which the local anesthetic is present at a concentration effective for inhibiting surgical miosis when introduced into an intraocular chamber.

Examples of suitable intraocular irrigation solutions are RINGERS solution, balanced salt solution and glutathione-bicarbonate-RINGERS solution. The preferred compositions and methods of preparation of suitable irrigation solutions have been disclosed in U.S. patent numbers 4,550,022 and 4,443,432 to Garabedian which are hereby incorporated by reference.

The preferred kit is a two-part irrigating product, including a stable, sterile prepackaged nonacidic (pH neutral or basic) solution and a stable, sterile prepackaged acidic solution. The nonacidic solution contains at least a nonphosphate buffer and is at pH 6.5 or above, preferably at about 7.4 pH. As used herein, pH neutral is 6.5 - 8.0 and basic is above 8.0 pH. Preferably the

buffer is acetate, bicarbonate, carbonate or citrate, or a combination thereof. The acid solution contains at least the 2-chloroprocaine, is free of dextrose and is at about pH 2.7-5.5. The acid solution may exist as a powder. In a most preferred embodiment, the nonacidic solution contains sodium ions, potassium ions, chloride ions, sodium bicarbonate, sodium citrate dihydrate and dextrose, while the acidic solution contains calcium chloride dihydrate, magnesium chloride hexahydrate, glutathione disulfide and 2-chloroprocaine hydrochloride. When mixed together, the solutions form a perfusion solution for irrigating the intraocular cavity during surgery, the perfusion solution containing between about 130 and 180 mM/l sodium ions, between about 3 and 15 mM/l potassium ions, between about 0.1 and 5 mM/l calcium ions, between about 0.1 and 5 magnesium ions, between about 2 and 10 mM/l dextrose, between about 0.03 and 1.0 mM/l oxidized glutathione or the equivalent amount of reduced glutathione, and a pH of about 6.5 to 8.0 and an osmolality of about 250 to 350 mOsm/kg. The most preferred two part solution is as follows:

Compound	Telor Neutral Solution Part I(mg/mL)	Telor Acidic Solution Part II(mg/mL)	Telor Reconstituted Solution Part I&II(mg/mL)
Sodium Chloride	7.44	0.00	7.14
Potassium Chloride	0.44	0.00	0.38
Calcium Chloride Dihydrate	0.00	3.85	0.15
Magnesium Chloride Hexahydrate	0.00	5.00	0.20
Sodium Bicarbonate	2.19	0.00	2.10
Sodium Citrate Dihydrate	1.77	0.00	1.70
Dextrose	0.96	0.00	0.92
Glutathione Disulfide	0.00	4.60	0.18
Chloroprocaine Hcl	0.00	7.5	0.30
Hydrochloride Acid and/or Sodium Hydroxide	to adjust pH	to adjust pH	
Volume	480 mL	20 mL	500 mL

In this formulation, the pH of Part I was adjusted to 7.45 and the pH of Part II adjusted to 3.28. When the products were combined, the final pH was 7.46 and the final osmolality was 306 MOsm.

Another two part solution is a liquid/powder system. In this system, the liquid Part I consists of the dextrose, buffering agents such as sodium citrate and sodium acetate, and electrolytes such as sodium chloride, potassium chloride, calcium chloride and magnesium chloride. Part II consists of the glutathione and chloroprocaine as a sterile powder in a smaller volume vial prepared by either lyophilizing, vacuum drying or some other equivalent technique. Part II may optionally also contain some bulking agents such as mannitol or some of the excipients found in the Part I solution such as sodium and potassium chloride.

The product is reconstituted by combining both parts together by means of a transfer spike and squeezing a portion of the Part I fluid into the Part II bottle and releasing. The fluid and powder (already partly dissolved) will then return to the large Part I bottle. Repeat this "squeeze and release" several times to flush all contents of the Part II bottle into the Part I bottle. Manually agitate the Part I bottle for about five (5) seconds or until all of the powder from the Part I bottle has gone into solution.

The kits may include instructions for preparation of a carrier or irrigation solution. The instructions may detail the use of the halogen substituted ester local anesthetic or solution in an intraocular chamber in connection with inhibiting surgical miosis. They also may include useful additional implements for mixing the contents of the containers in the kits or for delivery of the final therapeutic solution to an intraocular chamber.

The present invention also sets forth a device comprising a bottle, such as a wash bottle or an irrigation bottle, containing an intraocular irrigation solution including a halogen substituted ester local anesthetic present in an amount effective for inhibiting miosis or producing mydriasis when instilled into an intraocular chamber of an eye during intraocular surgery. The bottle preferably is formed from glass, but may also be rigid or flexible plastic and may be a bag. The device is useful for instilling or perfusing a solution in an intraocular chamber during surgery. A bottle suitable for wash or injection preferably contains 10ml to 50ml of the ocular irrigating solution and preferably contains the local anesthetic at a concentration between about 0.1mM and 10mM. A bottle suitable for use in perfusion of an intraocular cavity contains at least 100 ml of the intraocular irrigation solution and preferably contains the local anesthetic at a concentration between about 1 micromolar to 10mM.

Example 1

Lens removal surgery in dogs. All dogs underwent a presurgical work up including a complete physical exam, a complete ocular exam, an intraocular pressure measurement and a pupil measurement using a hand-held caliper (measured to the nearest millimeter).

The dogs were treated with the following anti-inflammatory regimen: on the morning before surgery, the dogs were given 0.5 mg/lb prednisone PO, one drop of 0.1% dexamethazone with neomycin and polymixin B (AK-Trol™) and 0.25 mg/lb flunixin meglumine IV. Beginning one hour before surgery, and every 15 minutes thereafter up until surgery, one drop of AK-Trol was applied topically. Post-operatively, QID one drop 0.1% AK-Trol Sx day. This was repeated at 1, 2 and 3 days post-operatively.

Surgical removal of the lens was performed using the techniques of phacoemulsification in mongrel dogs of either sex. General anesthesia was induced by intravenous Pentothal (25mg/ml, at a dose of 8mg/lb) and maintained by inhalation with isoflurane. The surgical site was prepared, draped and washed with BETADINE. Surgery was

performed on one eye, then the other. Lactated RINGERS solution was administered IV during the procedure, 4ml/lb/hr.

The surgical procedures were performed by observation through a surgical microscope. The anterior chamber was entered at the limbus and an anterior capsulotomy was performed. Using the phacoemulsification probe and irrigation/aspiration, the lens content material was broken up and removed from the eye. The irrigation solution was a balanced salt solution containing either the drug substance or a vehicle control. Over 15-20 minutes of surgical time, 100-400 mls of irrigation solution were delivered. Pupil size was monitored under the surgical microscope with the hand-held caliper.

At the end of surgery, the eye was closed with sutures and surgery on the other eye was performed similarly. When the second procedure was completed, the animal was allowed to recover. Post-operative inflammation was measured with a KOWA?T? Flarmeter for 72 hours after surgery.

Using the foregoing protocol, three dogs were treated in one eye with a vehicle and in the other eye with a perfusion solution containing 1 millimolar 2-chloroprocaine hydrochloride. The results are shown in Fig. 1, which demonstrates that pupil size was increased markedly in response to 2-chloroprocaine between the 10 and 25 minute interval after the initiation of the surgical procedure. (The perfusion solution was applied beginning at approximately seven minutes). The results were as follows:

TABLE 1
Pupil Diameter (mm)

Time (minutes)	2-Chloroprocaine (1mM)	Placebo
Pre-Operative	10.30	10.33
Post-Anesthesia	2.50	2.50
0	3.00	3.33
5	3.25	4.00
10	7.75	4.00
15	9.00	5.21
20	9.50	4.93
25	10.33	4.75
Post-Closure	7.83	4.33

Solutions containing 0.7 millimolar, 0.3 millimolar and 0.1 millimolar 2-chloroprocaine hydrochloride also were tested (data not shown). The 0.7 and 0.3 millimolar

solutions resulted in a marked increase in pupil size 3 minutes after the start of perfusion during surgery. A very slight effect was observed with the 0.1 solution.

Example 2

The effect of 2-chloroprocaine hydrochloride on post-operative intraocular pressure (IOP) was measured. No statistical differences were apparent between the eyes treated with 2-chloroprocaine hydrochloride and the eyes treated with the placebo. The results are shown in Fig. 2.

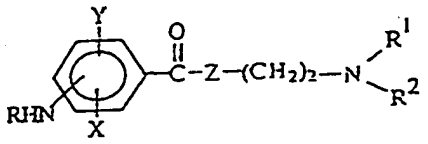
Example 3

The effect of 2-chloroprocaine hydrochloride on post-operative pupil size also was measured. Through 72 hours post-operatively, the pupil size of the chloroprocaine treated eyes was about 0.5mm larger than the pupil size of the placebo treated eyes. The results are shown in Fig. 3.

While the invention has been described in terms of preferred embodiments, those of ordinary skill in the art will recognize that modifications and equivalents may be made without departing from the scope of the present invention which is limited only by the following claims:

CLAIMS

1. A method for inhibiting intraoperative miosis or producing intraoperative mydriasis comprising introducing into an intraocular chamber of a subject, substantially simultaneously with performing intraocular surgery on said subject, an amount of a halogen substituted ester local anesthetic effective for inhibiting surgical miosis or producing intraoperative mydriasis, the anesthetic having the general formula:



where R is hydrogen or lower alkyl (1 to 4 carbon atoms, straight chain), R^1 is hydrogen or lower alkyl (1-4 carbon atoms, straight chain), R^2 is lower alkyl (1-4 carbon atoms) and may be straight chain or branched, X and Y are independently hydrogen, chloro or bromo, Z is oxygen or sulfur and with the proviso that the amino group (RHN-) may be present or absent and if present is substituted in the 3 or 4 position of the benzene ring.

2. The method of claim 1 wherein said local anesthetic is selected from the group consisting of 2-chloroprocaine, clormecaine, 2-bromoprocaine, 2-chlorotetracaine, 2-sec-butylaminoethyl-2-chloro-4-amino-benzoate, 2-tert-butylaminoethyl-2 chloro-4-amino benzoate, 2-chlorothiocaine, 2-diethylaminoethyl-3,4 dichlorobenzoate, 3,5 dichloroprocaine, 2,6 dichloroprocaine and 2-isobutylaminoethyl-2-chloro-4-amino-benzoate.

3. The method of claim 1 wherein said local anesthetic is introduced into said intraocular chamber by perfusing said chamber during intraocular surgery with an intraocular irrigating solution containing said local anesthetic.

4. The method of claim 3 wherein said local anesthetic is introduced into said intraocular chamber by perfusing said chamber during intraocular surgery with an intraocular irrigating solution that is free of a phosphate buffer.

5. The method of claim 1 wherein said local anesthetic is introduced into said intraocular chamber by injection of a pharmacologically acceptable carrier containing said local anesthetic into said intraocular chamber.

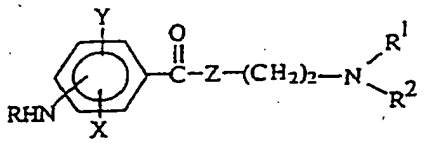
6. The method of claim 5 wherein said pharmacologically acceptable carrier is free of a phosphate buffer.

7. The method of claim 3, 4, 5 or 6 wherein said local anesthetic is 2-chloroprocaine hydrochloride.

8. A kit for intraocular surgery comprising a package including:

a. a first container containing a first amount of an ophthalmologically acceptable carrier, the first amount being between 10ml and 1000ml; and

b. a second container containing a local anesthetic in a concentrated amount, the local anesthetic having the following formula:



where R is hydrogen or lower alkyl (1 to 4 carbon atoms, straight chain), R^1 is hydrogen or lower alkyl (1 to 4 carbon atoms, straight chain), R^2 is lower alkyl (1-4 carbon atoms) and may be straight chain or branched, X and Y are independently hydrogen, chloro or bromo, Z is oxygen or sulfur and with the proviso that the amino group (RHN-) may be present or absent and if present is substituted in the 3 or 4 position of the benzene ring, and

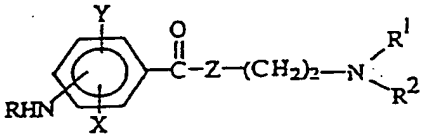
wherein when the first amount is mixed with the concentrated amount to produce an ophthalmologically acceptable solution, the local anesthetic is present in said ophthalmologically acceptable solution at a concentration effective for inhibiting intraoperative miosis or producing intraoperative mydriasis when perfused in an intraocular chamber.

9. A kit for providing an irrigant for intraocular surgery comprising a

package including:

a. a first container containing an irrigation amount of an intraocular irrigation solution, wherein the solution is incomplete with respect to one or more irrigant components, the irrigation amount being between 100 ml and 1000 ml; and

b. a housing containing a local anesthetic in a concentrated amount and containing said one or more irrigant components in a supplement amount, said local anesthetic having the following formula:



where R is hydrogen or lower alkyl (1 to 4 carbon atoms, straight chain), R^1 is hydrogen or lower alkyl (1-4 carbon atoms, straight chain), R^2 is lower alkyl (1-4 carbon atoms) and may be straight chain or branched, X and Y are independently hydrogen, chloro or bromo, Z is oxygen or sulfur and with the proviso that the amino group (RHN-) may be present or absent and if present is substituted in the 3 or 4 position of the benzene ring.

wherein, when the irrigation amount is mixed with the concentrated amount and with the supplement amount to produce an ophthalmologically acceptable solution, the local anesthetic is present in said ophthalmologically acceptable solution at a concentration effective for inhibiting intraoperative miosis or producing intraoperative mydriasis when perfused into an intraocular chamber during intraocular surgery, and said ophthalmologically acceptable solution is pH and osmotically compatible with intraocular tissues.

10. A kit for producing an irrigant for intraocular surgery as claimed in claim 9, wherein said housing is two containers, a second container containing said one or more irrigant components in the supplement amount; and a third container containing the local anesthetic in the concentrated amount.

11. The kit of claim 8 or 9 further comprising instructions for preparation of

said ophthalmologically acceptable solution and for use of said ophthalmologically acceptable solution as an irrigant during intraocular surgery.

12. The kit of claim 8 or 9 wherein said ophthalmologically acceptable solution is a water solution containing components selected from members of the group consisting of sodium ion, potassium ion, calcium ion, magnesium ion, chloride ion, acetate ion, bicarbonate ion, citrate ion, dextrose and glutathione disulfide, said solution being adjusted to a pH of between 6.5 and 8 and where the water solution is free of phosphate ion.

13. The kit of claim 8 or 9 wherein said local anesthetic is 2-chloroprocaine hydrochloride.

14. A device comprising a bottle containing an intraocular irrigating solution and a local anesthetic present in an amount effective for inhibiting miosis when perfused into an intraocular chamber of an eye during intraocular surgery.

15. The device claimed in claim 14 wherein said bottle contains at least 100ml of said intraocular irrigating solution.

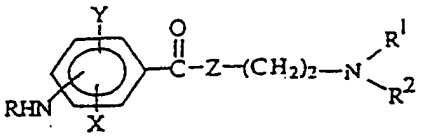
16. The device of claim 15 wherein said bottle contains a local anesthetic at a concentration between 0.1mM and 10mM.

17. The device of claim 16 wherein said local anesthetic is 2-chloroprocaine hydrochloride.

18. A two part tissue irrigating product comprising

a stable, sterile, prepackaged pH neutral solution that is buffered but is free of phosphate buffer, and

a stable sterile prepackaged acidic solution that contains a labile ester such as a local anesthetic of the following formula:



where R is hydrogen or lower alkyl (1 to 4 carbon atoms, straight chain), R^1 is hydrogen or lower alkyl (1-4 carbon atoms, straight chain), R^2 is lower alkyl (1-4 carbon atoms) and may be straight chain or branched, X and Y are independently hydrogen, chloro or bromo, Z is oxygen or sulfur and with the proviso that the amino group (RHN-) may be present or absent and if present is substituted in the 3 or 4 position of the benzene ring.

wherein the acidic solution is free of dextrose, at least one of the solutions containing sodium ions, at least one of the solutions containing chloride ions and at least one of the solutions containing potassium ions, wherein said acidic and nonacidic solutions when mixed together forming an ophthalmologically acceptable solution for use as an ophthalmic irrigant.

19. A two part product as in claim 18 wherein the acidic component contains glutathione and the nonacidic solution contains a buffer selected from the group consisting of acetate buffer, citrate buffer, carbonate buffer and bicarbonate buffer.

20. A two part product as claimed in claims 18 or 19 wherein the labile ester is a local anesthetic and wherein the ophthalmologically acceptable solution contains an effective amount of the local anesthetic for inhibiting surgical miosis or producing intraoperative mydriasis.

21. A two part product as in claim 20 wherein the local anesthetic is 2-chloroprocaine hydrochloride.

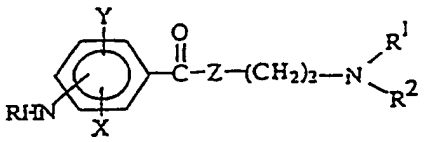
22. A two part product as in claim 18 wherein the acidic solution contains calcium ions, magnesium ions, glutathione and a halogen substituted local anesthetic, and the nonacidic solution contains sodium ions potassium ions, chloride ions, dextrose and at least one of an acetate and citrate buffer.

23. A two part tissue irrigating product comprising

a stable, sterile, prepackaged nonacidic solution that is buffered but is

free of phosphate buffer, and

a stable sterile prepackaged lyophilized powder that contains a labile ester such as a local anesthetic of the following formula:



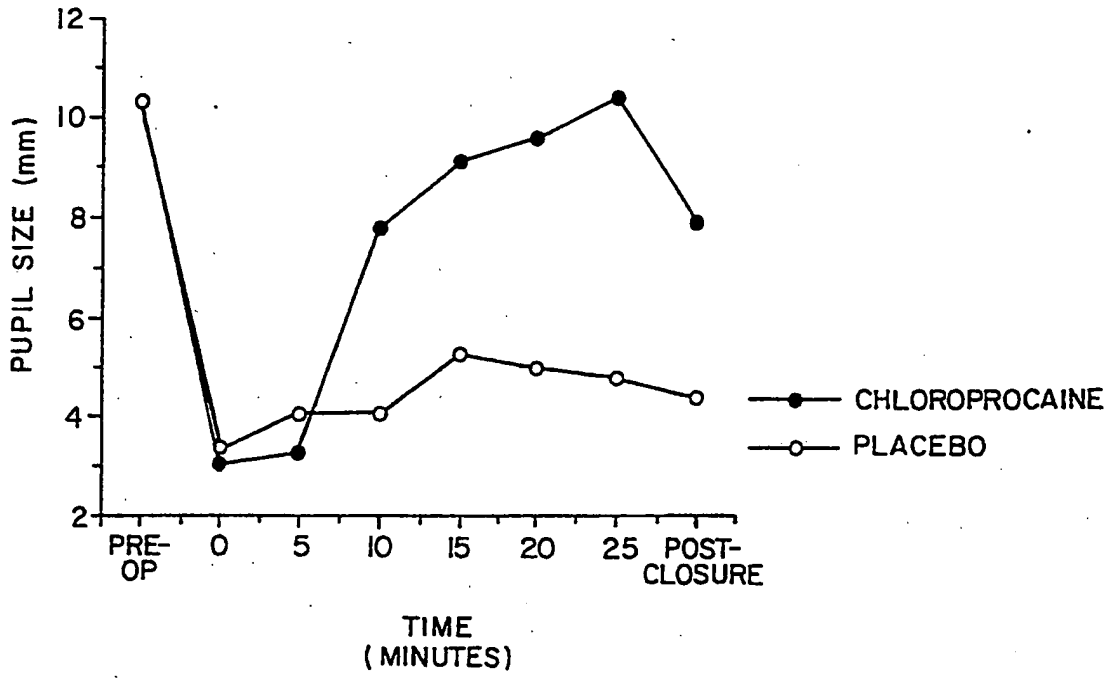
where R is hydrogen or lower alkyl (1 to 4 carbon atoms, straight chain), R^1 is hydrogen or lower alkyl (1-4 carbon atoms, straight chain), R^2 is lower alkyl (1-4 carbon atoms) and may be straight chain or branched, X and Y are independently hydrogen, chloro or bromo, Z is oxygen or sulfur and with the proviso that the amino group (RHN-) may be present or absent and if present is substituted in the 3 or 4 position of the benzene ring.

wherein at least one of the solution and powder containing sodium ions, at least one of the solution and powder contain chloride ions and at least one of the solution and powder containing potassium ions, wherein said solution and powder when mixed together form an ophthalmologically acceptable solution for use as an ophthalmic irrigant.

24. A two part product as in claim 23 wherein the powder contains glutathione and the nonacidic solution contains a buffer selected from the group consisting of acetate buffer, citrate buffer, carbonate buffer and bicarbonate buffer.

25. A two part product as claimed in claims 23 or 24 wherein the labile ester is a local anesthetic and where the ophthalmologically acceptable solution contains an effective amount of the local anesthetic for inhibiting surgical miosis or producing intraoperative mydriasis.

26. A two part product as in claim 25 wherein the local anesthetic is 2-chloroprocaine hydrochloride.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6
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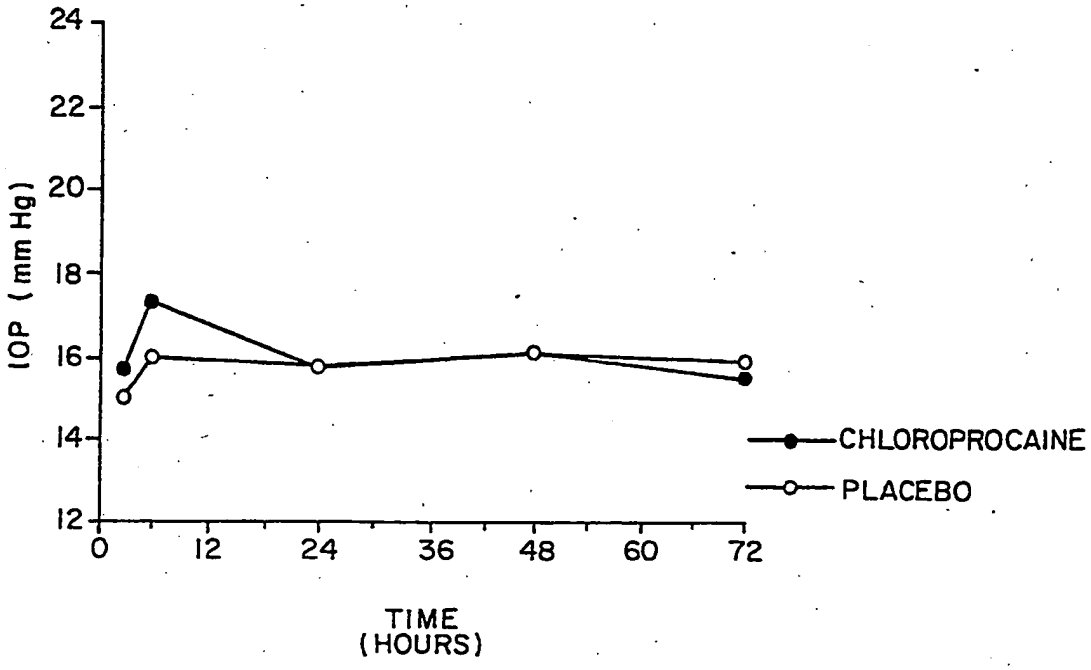
POST-CLOSURE
TIME (MINUTES)
CHLOROPROCAINE
PLACEBO

Fig. 1


IOP (mm Hg)
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22
20
18
16
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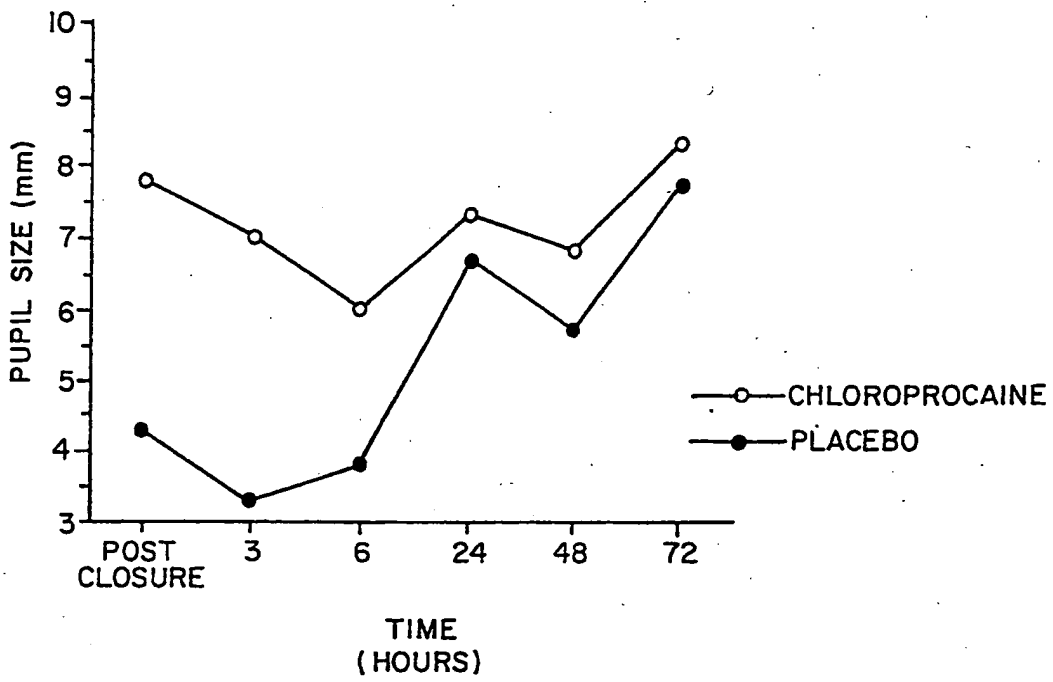
60
72
TIME (HOURS)
CHLOROPROCAINE
PLACEBO

Fig. 2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48
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TIME (HOURS)
CHLOROPROCAINE
PLACEBO

Fig. 3

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 95/07525

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BR. J. OPHTHALMOL., vol. 68, no. 4, 1984 pages 248-251, G. VAN RIJ ET AL. 'effect of oxybuprocaine 0.4% in preventing surgically induced miosis.' ---	
A	OPHTHALMOLOGY, vol. 89, no. 8, 1982 pages 966-979, R.M. DUFFIN ET AL. 'Inhibitors of surgically induced miosis.' --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 1995	26.09.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Klaver, T

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INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 95/07525

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANN. OPHTHALMOL., vol. 16, no. 10, 1984 pages 919-921, R.H. KEATES ET AL. 'Clinical trial of flurbiprofen to maintain pupillary dilation during cataract surgery.' ---	
A	US,A,4 938 970 (HUSTEAD ET AL.) 3 July 1990 -----	

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/US 95/07525

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4938970	03-07-90	NONE	